Use of central cannabinoid receptor antagonists for the preparation of drugs.

The present invention relates to a novel use of antagonists of the central cannabinoid receptors or so-called CB_1 receptors.

More particularly, the invention relates to the use of CB_1 receptor antagonists for the preparation of drugs useful in the treatment of appetency disorders. The purpose of drugs useful in the treatment of appetency disorders is to regulate consumption desires, particularly desires to consume sugars, carbohydrates, alcohol or drugs and more generally to consume appetizing ingredients.

In the present description and in the claims, appetency disorders are understood as meaning:

- disorders associated with a substance and especially abuse of a substance and/or dependency on a substance,

- disorders of food behaviors, especially those liable to cause excess weight, irrespective of its origin, for example : bulimia, appetency for sugars, non-insulin-dependent diabetes.

Substances are understood as meaning appetizing ingredients such as sugars, carbohydrates, alcohols or drugs.

The present invention therefore further relates to the use of a CB_1 receptor antagonist for the preparation of drugs useful in the treatment of bulimia and obesity, including obesity associated with type II diabetes (non-insulin-dependent diabetes), or more generally any disease resulting in the patient becoming overweight, and in the treatment of drug abuse or drug dependency.

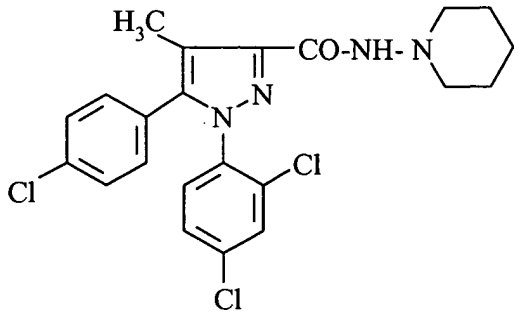
Delta-9-tetrahydrocannabinol, or Δ^9-THC, is the main active constituent extracted from Cannabis sativa (Tuner, 1985; in Marijuana, 84, Ed. Harvey, DY, IRL Press, Oxford).

The effects of cannabinoids are due to an interaction with high affinity specific receptors coupled to G proteins. Two types of receptors are currently described: the CB_1 receptors, which are present predominantly in the central nervous system (Devane et al., Molecular Pharmacology, 1988, 34, 605 - 613), and the CB_2 receptors, which are present in the immune system (Nye et al., The Journal of Pharmacology and Experimental Therapeutics, 1985, 234, 784 - 791; Kaminski et al., 1992, Molecular Pharmacology, 42, 736 - 742; Munro et al., Nature, 1993, 365, 61 - 65). Characterization of these receptors has been made possible by the development of synthetic ligands such as CP 55,940 (J. Pharmacol. Exp. Ther., 1988, 247, 1046 - 1051) and WIN 55212-2 (J. Pharmacol. Exp. Ther., 1993, 264,

1352 - 1363) and, more recently, by the discovery of the selective CB_1 receptor antagonist SR 141716 A (M. Rinaldi-Carmona et al., FEBS Lett., 1994, 350, 240-244).

Families of compounds having an affinity for the cannabinoid receptors have been described in several patents or patent applications, especially European patent application EP-576 357, which describes pyrazole derivatives, and patent application WO 96/02248, which describes especially benzofuran derivatives.

More particularly, N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide, also called SR 141716, of the formula



(I)

its pharmaceutically acceptable salts and their solvates are described in European patent application EP-656 354 as CB_1 central receptor antagonists.

SR 141716 A is the hydrochloride of SR 141716.

It is known that delta-9-tetrahydrocannabinol, whose international non-proprietary name is Dronabinol, is used in the treatment of anorexia, especially in patients suffering from AIDS (J. Pain Symptom Manage., 1995, 10 (2), 89 - 97) or cancer (J. Palliat. Care, 1994, 10 (1), 14 - 18).

It is further described that SR 141716 and its salts, which are central cannabinoid receptor antagonists, can be used in the treatment of appetite disorders, especially as anorexigenic agents, and in the treatment of disorders associated with the use of psychotropic substances.

Conventional anorexigenic agents cause an appetite reduction which is generally independent of the foods to be consumed.

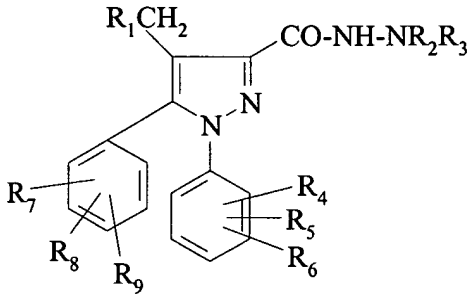
Surprisingly, it has now been found that CB_1 receptor antagonists have a specific property by acting electively on consumption behavior disorders pertaining to appetizing substances.

Thus the administration of a CB_1 receptor antagonist makes it possible to regulate the desire to consume non-essential food items such as excess sugars, excess carbohydrates, alcohol or drugs.

In fact, after having conducted tests in animals, a novel behavior of the animal has been noted : animal tests have revealed a novel behavior: the animal no longer shows spontaneous appetency for the ingredient, for example sugar or alcohol, which usually brings pleasure to it. This lack of appetency also manifests itself when the animal has been pretreated with a neuropeptide known to increase the appetite, for example neuropeptide Y (NPY).

According to one of its aspects, the present invention relates to the use of a CB_1 receptor antagonist for the preparation of drugs useful in the treatment of appetency disorders.

The CB_1 receptor antagonists appropriate for the purposes of the invention are particularly the compounds of the formula



(II)

in which:

- R_1 is hydrogen, a fluorine, a hydroxyl, a (C_1-C_5)alkoxy, a (C_1-C_5)alkylthio, a hydroxy(C_1-C_5)alkoxy, a group $-NR_{10}R_{11}$, a cyano, a (C_1-C_5)alkylsulfonyl or a (C_1-C_5)alkylsulfinyl;
- R_2 and R_3 are a (C_1-C_4)alkyl or, together with the nitrogen atom to which they are bonded, form a saturated or unsaturated 5- to 10-membered heterocyclic radical which is unsubstituted or monosubstituted or polysubstituted by a (C_1-C_3)alkyl or by a (C_1-C_3)alkoxy;
- R_4, R_5, R_6, R_7, R_8 and R_9 are each independently hydrogen, a halogen or a trifluoromethyl, and if R_1 is a fluorine, R_4, R_5, R_6, R_7, R_8 and/or R_9 can also be a fluoromethyl, with the proviso that at least one of the substituents R_4 or R_7 is other than hydrogen; and

- R_{10} and R_{11} are each independently hydrogen or a $(C_1$-$C_5)$alkyl, or R_{10} and R_{11}, together with the nitrogen atom to which they are bonded, form a heterocyclic radical selected from pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl and piperazin-1-yl, which is unsubstituted or substituted by a $(C_1$-$C_4)$alkyl,

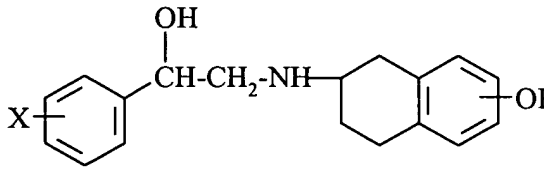
and their salts and their solvates.

More particularly, the present invention relates to the use of N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide, its pharmaceutically acceptable salts and their solvates for the preparation of drugs useful in the treatment of appetency disorders.

According to the present invention, the CB_1 receptor antagonists can also be used in association with another active principle for the preparation of drugs useful in the treatment of appetency disorders, especially in the treatment of disorders of food behaviors; it is possible to use a pharmaceutical composition comprising a CB_1 receptor antagonist in association with a compound for regulating metabolic disorders, especially a β_3-adrenergic receptor agonist, hereafter called a β_3-agonist.

Thus the present invention further relates to pharmaceutical compositions containing a CB_1 receptor antagonist and a regulator of metabolic disorders, for example a hypolipemic, hypolydemic or lipolytic. More particularly, the present invention relates to pharmaceutical compositions containing a CB_1 receptor antagonist and a β_3-agonist.

β_3-agonists which can be used according to the present invention are the compounds of the formula



(III)

in which:

- X is hydrogen, a halogen, a trifluoromethyl or a $(C_1$-$C_4)$alkyl;
- R is hydrogen or a methyl which is unsubstituted or substituted by a carboxyl or an alkoxycarbonyl in which the alkoxy is $(C_1$-$C_6)$,

and their pharmaceutically acceptable salts, indicated in EP 0 211 721 and EP 0 303 546 as intestinal spasmolytics.

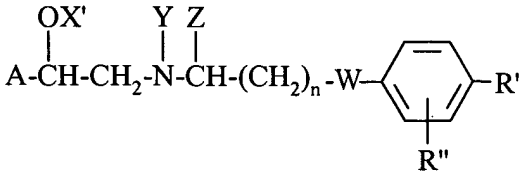
Among the compounds of formula (III), the following compounds:

* 2-[(7-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)amino]-1-phenylethanol;
* 2-[(7-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)amino]-1-(3-chlorophenyl)-ethanol;
* 2-[(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl)amino]-1-(3-chlorophenyl)ethanol;
* 2-[(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl)amino]-1-phenylethanol;
* (1R,2'RS)-2-[(7-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)amino]-1-phenyl-ethanol;
* (1S,2'RS)-2-[(7-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)amino]-1-phenyl-ethanol;
* (+)-(1R)-2-[(7-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)amino]-1-phenyl-ethanol;
* (+)-(1S)-2-[(7-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)amino]-1-phenyl-ethanol;
* (-)-(1R)-2-[(7-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)amino]-1-phenyl-ethanol;
* (-)-(1S)-2-[(7-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)amino]-1-phenyl-ethanol;
* N-[(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-(3-chlorophenyl)-2-hydroxyethanamine; and
* N-[(2R)-7-methoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-(3-chlorophenyl)-2-hydroxyethanamine,

and their pharmaceutically acceptable salts, are particularly advantageous.

N-[(2S)-7-Ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-(3-chlorophenyl)-2-hydroxyethanamine (SR 58611) and its pharmaceutically acceptable salts are very particularly advantageous, especially its salt with hydrochloric acid, SR 58611 A.

Other β_3-agonists which can be used according to the present invention are the compounds of the formula



(IV)

in which:

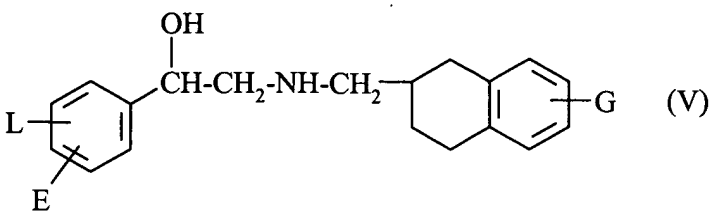
- n is 1, 2 or 3;
- A is a benzofuran-2-yl or a phenyl which is unsubstituted or substituted by one or two halogen atoms or by a (C_1-C_4)alkyl or a trifluoromethyl;
- R′ is:
  - hydrogen;
  - a (C_1-C_6)alkyl;
  - a functional group selected from the following groups: hydroxyl; (C_1-C_6)-alkoxy; (C_2-C_6)alkenyloxy; (C_2-C_6)alkynyloxy; (C_3-C_8)cycloalkoxy; (C_3-C_8)cycloalkyl(C_1-C_6)alkoxy; benzyloxy; phenoxy; mercapto; (C_1-C_6)alkylthio; (C_2-C_6)alkenylthio; (C_2-C_6)alkynylthio; (C_3-C_8)cycloalkylthio; (C_3-C_8)cycloalkyl(C_1-C_6)alkylthio; benzylthio; phenylthio; (C_1-C_6)alkylsulfinyl; (C_2-C_6)alkenylsulfinyl; (C_2-C_6)alkynylsulfinyl; (C_3-C_8)cycloalkylsulfinyl; (C_3-C_8)cycloalkyl(C_1-C_6)alkylsulfinyl; benzylsulfinyl; phenylsulfinyl; (C_1-C_6)alkylsulfonyl; (C_2-C_6)alkenylsulfonyl; (C_2-C_6)alkynylsulfonyl; (C_3-C_8)cycloalkylsulfonyl; (C_3-C_8)cycloalkyl(C_1-C_6)alkylsulfonyl; benzylsulfonyl; phenylsulfonyl; cyano; nitro; amino which is unsubstituted or substituted by one or two identical or different radicals selected from (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, benzyl and phenyl groups; carboxyl; alkoxycarbonyl in which the alkoxy is (C_1-C_6); (C_2-C_6)-alkenyloxycarbonyl; (C_2-C_6)alkynyloxycarbonyl; (C_3-C_8)cycloalkoxycarbonyl; (C_3-C_8)cycloalkyl(C_1-C_6)alkoxycarbonyl; benzyloxycarbonyl; phenoxycarbonyl; or carbamoyl which is unsubstituted or substituted on the amino group by one or two identical or different radicals selected from (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)-cycloalkyl, (C_3-C_8)cycloalkyl(C_1-C_6)alkyl, benzyl and phenyl groups;
  - a group R‴ selected from the following groups: (C_1-C_6)alkyl substituted by a functional group; (C_2-C_6)alkenyl substituted by a functional group; (C_2-C_6)-alkynyl substituted by a functional group; phenyl(C_1-C_6)alkyl substituted on the phenyl by a (C_1-C_6)alkyl or by a functional group; phenyl(C_2-C_6)alkenyl substituted on the phenyl by a (C_1-C_6)alkyl or by a functional group; phenyl(C_2-C_6)alkynyl substituted on the phenyl by a (C_1-C_6)alkyl or by a functional group; benzyl substituted on the phenyl by a (C_1-C_6)alkyl or by a functional group; and

phenyl which is unsubstituted or substituted by a (C_1-C_6)alkyl or by a functional group, the functional group being as defined above;

- a group O-R‴, S-R‴, SO-R‴ or SO_2-R‴, in which R‴ is as defined above;
- a group NR‴R°, in which R‴ is as defined above and R° is hydrogen or is as defined above for R‴, or R‴ and R°, together with the nitrogen to which they are bonded, form a group selected from pyrrolidino, piperidino and morpholino groups;
- a group COOR‴ or a group CO-SR‴, in which R‴ is as defined above;
- a group CONR‴R°, in which R‴ is as defined above and R° is hydrogen or is as defined above for R‴, or R‴ and R°, together with the nitrogen to which they are bonded, form a group selected from pyrrolidino, piperidino and morpholino groups;
- a group SO_2NR‴R°, in which R‴ is as defined above and R° is hydrogen or is as defined above for R‴, or R‴ and R°, together with the nitrogen to which they are bonded, form a group selected from pyrrolidino, piperidino and morpholino groups;
- R″ is hydrogen; a halogen; a (C_1-C_6)alkyl; a functional group as defined above; a group OR‴, R‴ being as defined above; a group COOR‴, R‴ being as defined above; or a group CONR‴R°, in which R‴ is as defined above and R° is hydrogen or is as defined above for R‴, or R‴ and R°, together with the nitrogen to which they are bonded, form a group selected from pyrrolidino, piperidino and morpholino groups;
- W is a direct bond or an oxygen atom;
- X′ is hydrogen, a (C_1-C_6)alkyl or a (C_1-C_6)alkylcarbonyl;
- Y is hydrogen or a group A′-CH(OH)-CH_2-, A′ being identical to A but other than benzofuran-2-yl; or
- X′ and Y, taken together, form a methylene group optionally substituted by an alkoxycarbonyl in which the alkoxy is (C_1-C_6); an ethylene group optionally substituted by an oxo group; or a 1,3-propylene group;
- Z is hydrogen or a (C_1-C_6)alkyl,

and their pharmaceutically acceptable salts, indicated in EP 0 255 415 as intestinal spasmolytics.

Other β_3-agonists which can also be used according to the present invention are the compounds of the formula



(V)

in which:

- E is hydrogen, a (C_1-C_4)alkyl, a (C_1-C_4)alkoxy, a phenyl, a nitro, a halogen atom or a trifluoromethyl;
- L is hydrogen, a (C_1-C_4)alkyl, a (C_1-C_4)alkoxy, a phenyl, a nitro or a halogen atom; or E and L together are a group -CH=CH-CH=CH- or -CH_2-CH_2-CH_2-CH_2-; and
- G is hydrogen, a chlorine atom, a hydroxyl or a group OG', in which G' is a (C_1-C_4)alkyl which is unsubstituted or substituted by a hydroxyl, (C_1-C_4)alkoxy, (C_1-C_4)alkoxycarbonyl, carboxyl or (C_3-C_7)cycloalkyl; a (C_3-C_7)cycloalkyl; or a (C_2-C_4)alkanoyl,

and their pharmaceutically acceptable salts, indicated in EP 0 436 435 as intestinal spasmolytics.

Among the compounds of formula (V), N-[(2R)-(6-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)methyl]-(2R)-2-hydroxy-2-(3-chlorophenyl)ethanamine (SR 59104), N-[(2R)-(7-methoxy-1,2,3,4-tetrahydronaphth-2-yl)methyl]-(2R)-2-hydroxy-2-(3-chlorophenyl)ethanamine (SR 59119) and their pharmaceutically acceptable salts are particularly advantageous compounds.

Other advantageous β_3-agonists according to the present invention are the compound BRL 35135 described in EP 23385; the compound CL 316243 described in US 5 061 727; the compound AZ 002 described in EP 218440; the compound BMS 187257 described in US 5 321 036; the compound ZD 7114 described in EP 473 285; the compound RO 40-2148 described in Am. J. Clin. Nutr., 1992, 55 (1, Suppl.), 249S - 251S; and the products described in the following patents/patent applications: WO 96/35671, WO 96/35670, WO 96/ 16038, WO 96/04233, WO 95/33724, WO 95/29159, EP 659737, WO 95/04047, EP 516349, EP 473285, EP 23385, EP 21636, EP 7205, JP 08198866, JP 08165276, JP 08157470, WO 96/16938, EP 714883, WO 96/04234, US 5 488 064, US 5 482 971, US 5 491 134, WO 95/29159, WO 95/33724, ZA 9409874, WO 95/29903, US 5 461 163, WO 95/25104, EP 659737, JP 07112958,

WO 95/ 8527, WO 95/07284, JP 07025756, WO 95/03289, WO 95/04047, WO 95/01170, WO 94/29290, US 5 373 020, JP 06293664, WO 94/12166 and US 5 451 677.

For its use as a drug, a CB_1 receptor antagonist compound, by itself or in association with a β_3-agonist, must be formulated as a pharmaceutical composition.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, transdermal, local or rectal administration, the active principle, by itself or in association with another active principle, can be administered to animals and humans in unit forms of administration mixed with conventional pharmaceutical carriers. The appropriate unit forms of administration include oral forms such as tablets, gelatin capsules, powders, granules and solutions or suspensions to be taken orally, sublingual and buccal forms of administration, aerosols, implants, subcutaneous, intramuscular, intravenous, intranasal or intraocular forms of administration and rectal forms of administration.

In the pharmaceutical compositions of the present invention, the active principle or active principles are generally formulated in dosage units. The dosage unit contains from 0.5 to 1000 mg, advantageously from 1 to 500 mg and preferably from 2 to 200 mg of CB_1 receptor antagonist per dosage unit for daily administration.

In cases where 2 active principles are associated, the dosage unit contains from 0.5 to 600 mg, advantageously from 1 to 400 mg and preferably from 2 to 200 mg of CB_1 receptor antagonist compound and from 0.5 to 600 mg, advantageously from 2 to 400 mg and preferably from 10 to 250 mg of the other active principle, especially a β_3-agonist.

When a solid composition is prepared in the form of tablets, a wetting agent such as sodium laurylsulfate can be added to the micronized or non-micronized active principle(s) and the whole is mixed with a pharmaceutical vehicle such as silica, starch, lactose, magnesium stearate, talcum or the like. The tablets can be coated with sucrose, a variety of polymers or other appropriate substances, or else they can be treated so as to have a sustained or delayed activity and so as to release a predetermined amount of active principle continuously.

A preparation in the form of gelatin capsules is obtained by mixing the active principle or active principles with a diluent, such as a glycol or a glycerol ester, and incorporating the resulting mixture into soft or hard gelatin capsules.

A preparation in the form of a syrup or elixir can contain the active principle or active principles together with a sweetener, which is preferably calorie-free, methylparaben and propylparaben as antiseptics, a flavoring and an appropriate color.

The water-dispersible powders or granules can contain the active principle or active principles mixed with dispersants or wetting agents or with suspending agents such as polyvinylpyrrolidone or polyvidone, as well as with sweeteners or taste correctors.

Rectal administration is effected using suppositories, which are prepared with binders melting at the rectal temperature, for example cocoa butter or polyethylene glycols.

Parenteral administration is effected using aqueous suspensions, isotonic saline solutions or injectable sterile solutions containing pharmacologically compatible dispersants and/or solubilizing agents, for example propylene glycol or butylene glycol.

Thus, to prepare an aqueous solution for intravenous injection, it is possible to use a cosolvent, for example an alcohol such as ethanol or a glycol such as polyethylene glycol or propylene glycol, and a hydrophilic surfactant such as Tween® 80. To prepare an oily solution for intramuscular injection, the active principle can be solubilized with a triglyceride or a glycerol ester.

Transdermal administration can be effected using patches in multilaminar form or with a reservoir in which the active principle is in alcoholic solution.

The active principle or active principles can also be formulated as microcapsules or microspheres, optionally with one or more carriers or additives.

The active principle or active principles can also be presented in the form of complexes with a cyclodextrin, for example α-, β- or γ-cyclodextrin, 2-hydroxy-propyl-β-cyclodextrin or methyl-β-cyclodextrin.

Among the sustained release forms useful in the case of chronic treatments, it is possible to use implants. These can be prepared in the form of an oily suspension or in the form of a suspension of microspheres in an isotonic medium.

According to another aspect of the invention, the CB_1 receptor antagonist and the regulator of metabolic disorders, especially the β_3-agonist, can be administered simultaneously, sequentially or over a period of time in the treatment of appetency disorders, especially in the treatment of disorders of food behaviors.

The invention therefore further relates to a kit for the treatment of appetency disorders by the administration, simultaneously, sequentially or over a period of time, of a CB_1 receptor antagonist and a regulator of metabolic disorders, especially a β_3-agonist, in which kit said CB_1 receptor antagonist and said regulator of metabolic disorders, especially said β_3-agonist, are in separate compartments and optionally in different packagings.

More particularly, said kit contains N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide, one of its pharmaceutically acceptable salts or one of their solvates, and N-[(2S)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2R)-2-(3-chlorophenyl)-2-hydroxyethanamine or one of its pharmaceutically acceptable salts.

According to another of its aspects, the invention further relates to a method of treating appetency disorders, especially a method of treating disorders of food behaviors, which consists in administering, to a subject in need thereof, a (therapeutically) effective amount of a CB_1 receptor antagonist as defined above. Said CB_1 receptor antagonist can advantageously be used in association with a regulator of metabolic disorders, especially a β_3 agonist, as defined above. In particular, the CB_1 receptor antagonist and the regulator of metabolic disorders can be administered simultaneously, sequentially or over a period of time.

TEST No. 1: Effect of SR 141716 A on the intake of a sucrose solution in rats

The experiment is performed according to W.C. Lynch et al., Physiol. Behav., 1993, 54, 877 - 880.

Male Sprague-Dawley rats weighing 190 to 210 g are under a normal light cycle (from 7 am to 7 pm) and receive water and food ad libitum.

For 6 days, between 11 am and 3 pm, the food and the water bottles are withdrawn and the rats are given a 5% sucrose solution to drink.

Rats drinking less than 3 g of sucrose solution are eliminated.

On the seventh day the test is carried out according to the following procedure:

9 am: withdrawal of food,

10 am: oral administration of SR 141716 A,

11 am = T0: introduction of bottles containing a weighed sucrose solution, T0 + 1 hour, T0 + 2 hours, T0 + 3 hours, T0 + 4 hours: measurement of the sucrose consumption by weighing of the bottles.

TABLE 1

Treatment po	Number of rats	Consumption of sucrose solution in g			
		1 hour	2 hours	3 hours	4 hours
Vehicle 2 ml/kg	8	11.33 ± 2.50	17.74 ± 4.00	22.50 ± 4.83	28.34 ± 5.01
SR 141716 A 0.3 mg/kg	6	5.18 ± 1.61	9.18 ± 2.12	12.49 ± 4.47	16.10 ± 3.95
SR 141716 A 1 mg/kg	6	3.27* ± 1.40	3.61** ± 1.40	5.65* ± 2.23	7.43** ± 2.81
SR 141716 A 3 mg/kg	6	2.95* ± 1.20	5.41* ± 1.33	6.96* ± 2.15	8.58** ± 2.92

* $p < 0.05$; ** $p < 0.01$, Dunnett test

It is seen from the results reported in TABLE 1 that the administration of SR 141716 A very considerably reduces the consumption of aqueous sugar solution at or above a dose of 0.3 mg/kg.

TEST No. 2: Effect of SR 141716 A on the consumption of an alcohol solution in mice

Male C 57 BL 6 mice (Iffa-Credo) are isolated on the day of their arrival in an animal housing under a reverse cycle (night from 10 am to 10 pm) with 2 bottles filled with water. After 1 week, one of the bottles of water is replaced with a bottle filled with a 10% alcohol solution for 6 hours of the test. Each day, 30 minutes before the bottle of alcohol is introduced, the mice are treated subcutaneously with SR 141716 A. The amounts of alcohol and water consumed are measured after 6 hours. The test is repeated for 4 days.

TABLE 2

Treatment mg/kg/sc SR 141716 A	Number of mice	Amount of alcohol consumed in g on D4	Amount of water consumed in g
Vehicle	20	1.9 ± 0.1	1.1 ± 0.1
0.1	10	1.4 ± 0.2	1.1 ± 0.3
0.3	10	1.3 ± 0.2	1.1 ± 0.3
1	10	1.1 ± 0.2**	1.3 ± 0.1
3	10	1.0 ± 0.2**	1.6 ± 0.3

** $p < 0.01$, Dunnett test

The results show that the alcohol consumption decreases very substantially for the treated animals: from 1.9 ± 0.1 g for an untreated animal to 1.0 ± 0.2 g for an animal receiving 3 mg/kg of SR 141716 A; the water consumption increased in parallel: from 1.1 ± 0.1 to 1.6 ± 0.3 g.

EXAMPLE 1 Gelatin capsule containing a 1 mg dose of CB_1 receptor antagonist

Micronized SR 141716	1.00 mg
Corn starch	51.00 mg
Lactose monohydrate	103.33 mg
Polyvidone	4.30 mg
Sodium laurylsulfate	0.17 mg
Crosslinked sodium carboxymethyl cellulose	8.50 mg
Purified water: QS for wet granulation	
Magnesium stearate	1.70 mg

For a no. 3 opaque white gelatin capsule filled to 170 mg

EXAMPLE 2 Gelatin capsule containing a 10 mg dose of CB_1 receptor antagonist

Micronized SR 141716 A	10.00 mg
Corn starch	51.00 mg
Lactose monohydrate	94.33 mg
Polyvidone	4.30 mg
Sodium laurylsulfate	0.17 mg
Crosslinked sodium carboxymethyl cellulose	8.50 mg

Purified water: QS for wet granulation	
Magnesium stearate	1.70 mg

For a no. 3 opaque white gelatin capsule filled to 170 mg

EXAMPLE 3 Gelatin capsule containing a 30 mg dose of CB_1 receptor antagonist

Micronized SR 141716	30.00 mg
Corn starch	51.00 mg
Lactose monohydrate	74.33 mg
Polyvidone	4.30 mg
Sodium laurylsulfate	0.17 mg
Crosslinked sodium carboxymethyl cellulose	8.50 mg
Purified water: QS for wet granulation	
Magnesium stearate	1.70 mg

For a no. 3 opaque white gelatin capsule filled to 170 mg

EXAMPLE 4 Tablet containing a 30 mg dose of CB_1 receptor antagonist

Micronized SR 141716	30.00 mg
Lactose monohydrate	QS
Corn starch	40.00 mg
Hydroxypropyl methyl cellulose 6 cP	5.00 mg
Purified water: QS for wet granulation	
Crosslinked sodium carboxymethyl cellulose	10.00 mg
Magnesium stearate	2.00 mg

For a finished tablet of 200 mg

EXAMPLE 5 Tablet containing 30 mg of CB_1 receptor antagonist and 200 mg of β_3-agonist

Micronized SR 141716	30.00 mg
SR 58611 A expressed as the base	200.00 mg
Lactose monohydrate	QS
Polyvidone	15.00 mg
Purified water: QS for wet granulation	

Crosslinked sodium carboxymethyl cellulose	10.00 mg
Magnesium stearate	5.00 mg

For a finished tablet of 500 mg

EXAMPLE 6 Tablet containing 10 mg of CB_1 receptor antagonist and 100 mg of β_3-agonist

Micronized SR 141716	10.00 mg
SR 58611 A expressed as the base	100.00 mg
Corn starch	30 mg
Lactose monohydrate	QS
Hydroxypropyl methyl cellulose 6 cP	5.00 mg
Purified water: QS for wet granulation	
Sodium carboxymethyl starch	6.00 mg
Magnesium stearate	3.00 mg

For a finished tablet of 300 mg